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Working title: Long-term safety of siltuximab in patients with idiopathic multicentric Castleman disease: a prespecified, open label extension analysis of two trials

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ABSTRACT

Background

Siltuximab is recommended by international consensus as a first-line treatment for idiopathic multicentric Castleman disease on the basis of durable efficacy and safety data. This study was done to assess the long-term safety and activity of siltuximab over up to 6 years of treatment.

Methods

This study is a prespecified open-label extension analysis of a phase 1 trial (NCT00412321) and a phase 2 trial (NCT01024036), done at 26 hospitals worldwide. Patients in both studies were at least 18 years old with histologically confirmed, symptomatic Castleman disease. This extension study enrolled 60 patients who completed the previous trials without disease progression on siltuximab. Patients received siltuximab infusions of 11 mg/kg every 3 weeks (which could be extended to 6 weeks) for up to 6 years. Descriptive statistics were used to summarise the data. No formal hypothesis testing was performed. The primary endpoint was the safety of siltuximab, assessed at each dosing cycle. The study was registered with ClinicalTrials.gov, number NCT01400503 and with EudraCT, number 2010-022837-27.

Findings

Patient enrolment into the phase 1 trial was from June 20, 2005, to Sept 15, 2009, and enrolment into the phase 2 trial was from Feb 9, 2010, to Feb 3, 2012. Patients were enrolled in this long-term extension from April 1, 2011, to Jan 15, 2014. Median follow-up was 6 years (IQR 5·11–7·76). Median treatment duration, from the beginning of the previous trials to the end of the present study, was 5·5 years (IQR 4·26–7·14). Siltuximab was well tolerated; however, adverse events of grade 3 or worse were reported in 36 (60%) of 60 patients with the most common being hypertension (eight [13%]), fatigue (five [8%]), nausea (four [7%]), neutropenia (four [7%]), and vomiting (three [5%]). 25 (42%) patients reported at least one serious adverse event, which most commonly was an infection

(eight [13%]). Only two serious adverse events, polycythaemia and urinary retention, were considered related to siltuximab treatment. 18 patients discontinued before study completion, either to receive siltuximab locally (eight) or because of progressive disease (two), adverse events (two), or other reasons (six). No deaths were reported.

Interpretation

These results show that siltuximab is well tolerated long term and provides important evidence for the feasibility of the life-long use required by patients with idiopathic multicentric Castleman disease.

RESEARCH IN CONTEXT

Evidence before this study

On June 20, 2019, we searched PubMed for clinical trials using the terms “Castleman disease OR Castleman’s disease AND siltuximab”, filtered for “clinical trial” article type. The search yielded two trials: a phase 1 dose-finding study by Kurzrock and colleagues (NCT00412321) and a randomised phase 2 study reported by van Rhee and colleagues (NCT01024036). Both of the final analyses of these studies have previously been reported, in 2013 and 2014. An interim safety analysis of the open-label extension period of the phase 1 and 2 studies, reporting on 19 patients enrolled from the phase 1 study, was published by van Rhee and colleagues in 2015. These analyses have so far shown that siltuximab is an effective and well tolerated treatment for patients with idiopathic multicentric Castleman disease, with no apparent dose-related or cumulative toxic effects. The safety profile to date indicates thrombocytopenia, hypertriglyceridaemia, neutropenia, hypercholesterolaemia, and anaemia as the most common treatment-related adverse events. Serious adverse events were reported in 42–53% of patients across siltuximab treatment groups and in 54% of the placebo plus best supportive care group in the phase 2 trial. These data relate to 53 patients who had received siltuximab for a median of 12·3 months (IQR 6·2–19·8) in the phase 2 trial, 37 patients who had received siltuximab for a median of 22·0 months (8·0–39·5) in the phase 1 trial, and 19 patients who had received siltuximab for a median of 5·1 years (4·0–5·9) in the open-label extension (with 14 patients having been treated with siltuximab for more than 4 years).

Added value of the study

The IL6 inhibitor siltuximab is a disease-modifying drug approved for the treatment of idiopathic multicentric Castleman disease. Although effective at relieving symptoms by neutralising the effects of IL6 overproduction, it does not address the source of IL6 overexpression, and thus the duration of siltuximab therapy is not limited. Therefore, establishing the long-term safety and activity of

siltuximab is of crucial importance to the management of idiopathic multicentric Castleman disease. Here, we present the final data from the open-label extension study that included patients enrolled in the phase 1 and 2 trials. 60 patients with idiopathic multicentric Castleman disease were enrolled (19 from the phase 1 trial and 41 from the phase 2 trial), considerably increasing the patient numbers from the 19 reported in the interim open-label analysis. These patients were treated for a median treatment length of 5·5 years (IQR 4·26–7·14). This study, therefore, spans a longer period and involves a greater number of patients than any previous study investigating siltuximab, or indeed any drug for the treatment of idiopathic multicentric Castleman disease. Given the rarity of the disease and the need for life-long treatment, this study provides a valuable update to the data, supporting the long-term activity and safety of siltuximab treatment in patients with idiopathic multicentric Castleman disease.

Implications of all the available evidence

The results of this study show that siltuximab has an acceptable safety and tolerability profile when administered over a long period, with no evidence of cumulative toxicity within this time. 58 (97%) of 60 patients maintained or achieved disease control at their last on-study assessment, and 42 (70%) patients completed the study with disease control, providing evidence of long-term activity. Overall, this study reinforces the use of siltuximab as the first-choice treatment option, as per the international consensus idiopathic multicentric Castleman disease treatment guidelines.

INTRODUCTION

Multicentric Castleman disease is a rare, heterogeneous disorder characterised by generalised lymphadenopathy in multiple lymph node chains.[1] Although a causative role for human herpesvirus 8 (HHV-8) is well established, the cause remains obscure in up to two-thirds of patients,[2] who are thought to have distinct pathogenesis related to cytokine dysregulation.[3] In the clinic, management of HHV-8-negative multicentric Castleman disease or idiopathic multicentric Castleman disease[4] has been hindered by the unknown cause,[5] heterogeneous presentation,[2] absence of diagnostic markers,[2] poor prognosis,[6] and few treatment options that are mostly symptomatic and do not have high-quality supporting evidence.[1,6,7]

Progress in the management of idiopathic multicentric Castleman disease has stemmed from recognition of the importance of interleukin-6 (IL6) in the pathogenesis.[1,4,5] Of the multiple cytokines that are upregulated, IL6 is the most prominent and drives B-lymphocyte proliferation and increased vascular endothelial growth factor production.[1,4,8] These changes bring about lymphoma-like symptoms, increased tumour blood supply, and a proinflammatory syndrome associated with elevations in acute-phase reactants, systemic symptoms, and, in severe cases, multi-organ failure and death.[1,8,9] IL6 also directly contributes to some of the laboratory abnormalities seen in idiopathic multicentric Castleman disease—eg, via effects on iron metabolism (causing anaemia) and albumin production (causing hypoalbuminaemia).[1]

These observations provided a rationale for the evaluation of siltuximab—a chimaeric (human–murine) monoclonal antibody (mAb) with high affinity and specificity for human IL6—in patients with idiopathic multicentric Castleman disease.[8,10] Initial evidence was provided by a phase 1 dose-finding study[11] in 37 adults with symptomatic Castleman disease, which showed a high proportion of patients with a response and sustained suppression of C-reactive protein with various siltuximab dosing regimens.

On the basis of the phase 1 profile, pharmacokinetic and pharmacodynamic modelling, and the half-life of 20·6 days, a dosing regimen of 11 mg/kg every 3 weeks was selected for further development.[11]

In the randomised phase 2 trial[12] in patients with idiopathic multicentric Castleman disease, siltuximab 11 mg/kg every 3 weeks plus best supportive care provided durable tumour and symptomatic responses by independent assessment in 18 (34%) of 53 patients (compared with 0% with placebo plus best supportive care) after a median follow-up of 14 months (IQR 10–21). Siltuximab also showed acceptable safety, with few serious adverse events or discontinuations because of adverse events, and no evidence of new or cumulative toxicity.[12] Following these results, siltuximab became the only drug approved for idiopathic multicentric Castleman disease in North America and Europe.[5,13]

As siltuximab is a therapy for a chronic disease that might require life-long administration, it is important to address outstanding questions regarding its long-term safety (including the potential for cumulative toxicity) and activity (ie, the sustainability of response).[5] The development programme, therefore, included a long-term, open-label, safety extension study following on from the phase 1 and 2 studies.[14] A previous interim analysis indicated no dose-related or cumulative toxic effects, but was limited to patients entering after the phase 1 study (n=19) and was done 2 years after initiation of the extension.[14] Here, we report the final safety and activity data 6 years after the start of enrolment, in the full cohort of 60 patients.

METHODS

Study design and participants

This was a prespecified open-label extension analysis of patients who previously completed either the phase 1 dose-finding study (NCT00412321)[11] or the phase 2 placebo-controlled study (NCT01024036)[12] with stable or improved disease. It was done at 26 hospitals in Belgium, Brazil,

Canada, China, Egypt, France, Germany, Hong Kong, New Zealand, Norway, Singapore, South Korea, Spain, Taiwan, the UK, and the USA. The protocol and the list of trial sites are included in the appendix (pp 1–3, 9–81).

In the phase 1 dose-finding trial, 37 patients with Castleman disease were treated with siltuximab in cohorts ranging from 3 mg/kg every 2 weeks to 12 mg/kg every 2 weeks, with a median of 31 doses (IQR 14–58) for a median duration of 22·0 months (8·0–39·5; maximum 60·5 months).[11] In the phase 2 trial, 79 HIV-negative and HHV-8-negative patients with symptomatic multicentric Castleman disease were randomly assigned to receive either 11 mg/kg siltuximab (n=53) or placebo (n=26) every 3 weeks until treatment failure.[12] After treatment failure, patients assigned placebo had the option of switching to open-label siltuximab, 13 of whom did so, and, after three discontinuations,ten were continuing treatment at the time of the primary analysis. Six patients originally assigned to placebo were continuing to receive placebo at the time of the primary analysis.[12]

Except for two patients with unresectable unicentric disease included in the phase 1 trial, all patients had histologically confirmed, measurable, and symptomatic idiopathic multicentric Castleman disease.[11,12] All histological variants of idiopathic multicentric Castleman disease were permitted.[11,12] Patients were aged at least 18 years. Signs and symptoms were mild to moderate, with patients required to have a Karnofsky performance score of at least 60 in the phase 1 study and an Eastern Cooperative Oncology Group performance status of 0–2 in the phase 2 trial. Patients who were HIV-positive or HHV-8-positive, had other clinically significant infections including hepatitis B or C, had skin lesions as the sole measurable manifestation of multicentric Castleman disease, or had a previous lymphoma, were excluded. A full list of inclusion and exclusion criteria are provided in the study protocol (appendix pp 9–81). Patients in both studies could have been newly diagnosed or previously treated (provided no previous anti-IL6 therapy was received).[11,12] Only patients who had completed either preceding trial without progressive disease were included. This included patients

who had progressive disease on placebo and switched to siltuximab during the phase 2 trial and included patients who did not have progressive disease while taking either siltuximab or placebo alone from either trial. Participants must have had their last administration of study treatment (siltuximab or placebo) less than 6 weeks (window of plus 2 weeks) before and must have adequate laboratory test results in the 2 weeks before the first dose of treatment for this trial.

This trial had a data cutoff 6 years after the start of enrolment. At the end of the observation period, patients were transferred to local hospital care. For those without siltuximab access, the sponsor arranged continued supply.

All patients provided written informed consent and the study was approved by institutional review boards or ethics committees at all sites before initiation. The study was conducted per Good Clinical Practice guidelines and the Declaration of Helsinki.

Procedures

All patients received siltuximab 11 mg/kg every 3 weeks as a 1-h intravenous infusion until progressive disease, withdrawal of consent, unacceptable toxicity, or the 6-year data cutoff, whichever occurred first. At the investigator's discretion, patients showing partial response or complete response for longer than 6 months (including those entering the study in partial response or complete response) could switch to every 6 weeks dosing during either preceding study or the extension. If progressive disease was suspected in these patients, they were rescreened, assessed, and resumed on standard every 3 weeks dosing. Prestudy therapies administered up to 30 days before the first dose of study treatment were recorded at screening. Concomitant medications were recorded throughout the study. Other antitumour therapies for idiopathic multicentric Castleman disease or other biologics were not permitted.

Clinical and laboratory assessments of haemoglobin, fatigue, anorexia, fever, weight, and size of largest lymph node (table 1) were done during screening, at cycles 4, 7, and 10, every 6 months

thereafter, and at study treatment discontinuation. If a patient showed a worsening of these categories or progressive disease for two consecutive screenings, then they discontinued the study treatment. Data collection for discontinued patients was limited only to survival status, the occurrence of malignancies, and subsequent multicentric Castleman disease therapy. Triglyceride, neutrophil, platelet, and haemoglobin measurements were taken at baseline and every three cycles thereafter. A validated immunoassay was done in blood samples collected every 12 weeks during siltuximab treatment and at weeks 4, 8, and 12 after last administration.

Adverse events were assessed according to common terminology criteria for adverse events, version 4, at each dosing cycle.

Outcomes

The primary endpoint was the long-term safety of siltuximab, defined as the number of participants with adverse events, up to a maximum of 6 years of treatment.

Investigator assessment of disease control was performed and used for secondary endpoints assessing the proportion of patients achieving disease control, the duration of disease control, and overall survival. Disease control was defined as stability or improvement and no worsening in haemoglobin, fatigue, anorexia, fever, weight, and size of largest lymph node (table 1). Efficacy-related laboratory parameters (erythrocyte sedimentation rate [ESR], C-reactive protein, and fibrinogen) were also secondary endpoints. Assessment of the reliability of the multicentric Castleman disease symptom scale (MCDSS)[15] was also assessed. Reliability of the MCDSS is not reported here. Overall survival is also not reported because no patients died.

Other prespecified safety and efficacy endpoints were the changes from baseline in triglyceride, neutrophil, platelet, and haemoglobin amounts and the development of antibodies to siltuximab (immunogenicity) after long-term treatment in the multicentric Castleman disease population.

Statistical analysis

Descriptive statistics were used to summarise the data. No formal hypothesis testing was done. No power calculations or derivations of sample size were done for this study because the patient number was determined by the number of eligible patients from the phase 1 and 2 studies; it was expected that up to 75 patients could be enrolled. Endpoints were assessed in the overall population of previously treated patients and siltuximab-naive patients. The study was registered with ClinicalTrials.gov, number NCT01400503 and with EudraCT, number 2010-022837-27.

Role of the funding source

The funders had a role in study design, patient recruitment, data collection, data analysis, data interpretation, and writing of the report. FvR, CC, PMV, LEF, DG, KK, and RK had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Enrolment for the phase 1 and 2 trials was from June 20, 2005, to Sept 15, 2009,[11] and Feb 9, 2010, to Feb 3, 2012.[12] Between April 1, 2011, and Jan 15, 2014, 60 patients entered the extension study and were followed up until March 2, 2017 (figure). Patient characteristics at baseline of the preceding studies are summarised in table 2.

Median follow-up was 6 years (IQR 5·11–7·76). The median duration of siltuximab treatment, including treatment in the preceding phase 1 and 2 trials, was 5·5 years (IQR 4·26–7·14). 37 (62%) of 60 patients received study treatment for 5 years or longer. The median number of siltuximab administrations was 86 (IQR 61–112). Deviations from protocol during the study were recorded in 17 (28%) of 60 patients. Major deviations included safety assessment deviation (ten [17%] of 60), receiving the wrong treatment or incorrect dose (four [7%] of 60), efficacy assessment deviation (three [5%] of 60), and not satisfying the entry criteria (two [3%] of 60); these patients were included in all analyses. 18 patients discontinued before study completion, of whom eight continued

siltuximab locally (siltuximab became commercially available in the USA during the trial so some patients elected to receive treatment locally instead of travelling to study sites). The remaining ten patients discontinued because of withdrawal of consent (n=4), progressive disease (n=2), adverse events (n=2), physician's decision (n=1), and pregnancy (n=1).

During the study, 124 dose delays were recorded in 37 patients; 16 (27%) of 60 patients had one delay, four (7%) had two delays, and the remaining 17 (28%) had three or more. 53 (43%) of 124 delays were due to adverse events, and the remaining 71 (57%) were due to other reasons such as surgery unrelated to idiopathic multicentric Castleman disease, scheduling conflicts, or travel difficulties. Six (10%) patients had dose delays due to surgery, for obstructive micturition, gastric bypass, contusion, spinal stenosis and cataract, total abdominal hysterectomy for fibroids, and inguinal hernia (one each).

35 (58%) of 60 patients remained on the original dosing regimen of 11 mg/kg every 3 weeks, whereas 25 (42%) patients received 11 mg/kg every 6 weeks. Eight (32%) of these 25 patients entered the present study on the every 6 weeks regimen, whereas 17 (68%) transitioned to the every 6 weeks regimen during the study. Only one (4%) patient returned to the original dosing, after transitioning to the every 6 weeks regimen at cycle 5; the patient returned to every 3 weeks dosing at cycle 29 due to suspected progressive disease.

All patients reported at least one adverse event during the study. The most commonly reported adverse events (occurring in ≥20 patients) were upper respiratory tract infection in 40 (67%) of 60, fatigue in 31 (52%), diarrhoea in 23 (38%), nausea in 22 (37%), rash in 21 (35%), and arthralgia in 20 (33%; appendix p 4). 36 (60%) patients reported adverse events of grade 3 or worse. The most frequently reported (occurring in more than two patients) grade 3 or worse adverse events were hypertension in eight (13%), fatigue in five (8%), nausea in four (7%), neutropenia in four (7%), and vomiting in three (5%) patients (appendix p 4).

53 (88%) of 60 patients reported treatment-emergent adverse events (TEAEs) that were considered at least possibly related to siltuximab (table 3).

25 (42%) of 60 patients reported at least one serious adverse event. Serious adverse events related to infection were reported in eight (13%) patients, including pneumonia in two (3%) patients. Two serious adverse events were treatment related (one [2%] case of polycythaemia, which resolved after 5 days of hydration, and one [2%] urinary retention).

Two (3%) patients permanently discontinued siltuximab treatment due to adverse events. One patient had increased alanine transaminase at baseline and developed increases in aspartate transaminase and γ-glutamyl transferase that were considered treatment related. The other patient had chest injury, pneumothorax, and rib fracture due to an accident considered unrelated to siltuximab treatment. Two (3%) patients reported infusion-related TEAEs of maculopapular rash or flushing, neither of which exceeded grade 3 or led to discontinuation. No deaths were reported during the study. Patients treated with siltuximab had an exposure-adjusted incidence rate of serious infections of 20 per 1000 patient-years.

Most haematological and biochemical abnormalities were of maximum grade 2. Grade 3 haematological abnormalities included lymphocytopenia in five (8%) of 60 patients, anaemia in three (5%), neutropenia in three (5%), and leukopenia in two (3%). Grade 4 neutropenia was reported in one (2%) patient. Grade 2 thrombocytopenia was reported in one (2%) patient (no grade ≥3 thrombocytopenia was reported). Grade 3 biochemical abnormalities included increased aspartate transaminase in two (3%) patients and alanine transaminase in one (2%) patient. Increases in liver enzymes did not exceed grade 3 and led to discontinuation in the abovementioned patient. Increased creatinine at each grade 3 and grade 4 was recorded in one patient. Hypertriglyceridaemia was reported at grade 1–2 in 27 (45%) patients and at grade 3 in one (2%) patient. Hypertriglyceridaemia was manageable with lipid-modifying drugs, which were administered to 25 (42%) patients.

In total, three (5%) of 60 patients tested positive for anti-siltuximab antibodies, none of which were neutralising. Two (3%) patients had transient anti-siltuximab antibodies at a single timepoint, one of whom had crossed over from placebo to siltuximab. One (2%) patient showed persistent anti-siltuximab antibodies at all except two timepoints. None of the antibody responses affected activity, safety, or pharmacokinetics.

Of the 60 patients enrolled in the extension, two (3%) had progressive disease during the study (on days 196 and 577; table 4). Of the three patients who were siltuximab naive at the start of the extension, all completed the study with disease control. The median duration of disease control was not reached during the study. Durable disease control was recorded in 42 (70%) of 60 patients for up to 6 years, with 58 (97%) patients having disease control at their last on-study assessment.

Low-grade increases of triglycerides were common (grade 1 in 21 [35%] of 60 patients and grade 2 in six [10%] patients), but manageable with lipid-modifying drugs (appendix pp 7–8). The observed pattern of the mean values for triglycerides, haemoglobin, platelets, and neutrophils remained largely consistent post-baseline. The maximum mean increase from baseline in haemoglobin level was 6·7 g/L at cycle 28. Neutrophils and platelets showed a maximum mean decrease of $–0·6 \times 10^9$ cells per L (SD 1·7) at cycle 55 and $–38·5 \times 10^9$ cells per L (SD 61·1) at cycle 40 (appendix pp 7–8).

Sustained decreases in C-reactive protein, ESR, and fibrinogen were observed throughout the trial, and maximum changes were observed from cycle 1 (month 0) of the present trial to cycle 58 (appendix pp 5–6). ESR showed a maximum mean decrease of –25·7 mm/h (SD 39·5). C-reactive protein showed a maximum mean decrease of –26·9 mg/L (31·3) at cycle 58. Fibrinogen showed a maximum mean decrease of –2·77 µmol/L (3·2) from cycle 1 to cycle 58.

DISCUSSION

Idiopathic multicentric Castleman disease is a chronic disease[16] and siltuximab must be taken continuously to maintain remission.[17] Therefore, understanding the long-term safety and activity of

siltuximab is vital.[5] This long-term safety extension in patients who completed phase 1 or 2 siltuximab trials represents the longest analysis of siltuximab treatment in patients with idiopathic multicentric Castleman disease. Conservatively, a durable disease response was recorded in 42 (70%) of 60 patients for up to 6 years, with 58 (97%) patients having disease control at their last on-study assessment. Eight patients discontinued the study to receive siltuximab locally when it became commercially available in the USA, suggesting that they were continuing to benefit from and tolerate siltuximab. Although no subsequent response assessments were done, they might have achieved a response with continued treatment.[17] The new idiopathic multicentric Castleman disease response criteria published by van Rhee and colleagues[9] had not been formulated at the time of inception of this long-term safety study. Therefore, clinical activity was assessed in terms of disease control using the Clinical Benefit Response Criteria. Because the Clinical Benefit Response Criteria used do not include categories of complete or partial response, we are not able to report on those outcomes. These results are remarkable for a 3–6 weekly intravenous therapy after 6 years and provide further support for the first-line use of siltuximab, as recommended in consensus guidelines.[9]

Of the 60 patients enrolled, the incidence of grade 3 or worse TEAEs, serious adverse events, and discontinuations of treatment because of TEAEs remained quite low, and no deaths were reported. Because data collection was limited in the 18 discontinued patients, we imputed all discontinuations as treatment failures.

Importantly, sustained disease control was reached even with 25 (42% of 60 patients switching to every 6 weeks dosing. Although rigorous pharmacokinetic and pharmacodynamic analyses were not included in the extension study, the every 6 weeks dosing interval was selected on the basis of previous clinical observations of tolerability and maintenance of disease control in patients who missed a dose on the per-protocol every 3 weeks schedule (and thereby received de facto every 6 weeks dosing). The potential for extending the dosing interval is particularly relevant given the need for long-term intravenous therapy, but additional studies are needed to examine the potential to

further optimise the dosing and duration of siltuximab therapy in patients with idiopathic multicentric Castleman disease.

Notably, siltuximab treatment might falsely increase IL6 concentrations for many months after the last dose because siltuximab–IL6 complexes interfere with current immunological IL6 quantification methods.[9] Additionally, siltuximab might interfere with IL6 quantification methods.[7,18,19] Therefore, serum IL6 concentrations should not be used to assess response to treatment. Instead, C-reactive protein has been identified as a surrogate biomarker for IL6 activity, because its production by hepatocytes is fully dependent on IL6 in vivo.[19] Siltuximab treatment in the present study showed a sustained decrease in C-reactive protein values from cycle 1 to cycle 58 of treatment; a decrease from baseline in C-reactive protein values was observed until cycle 66. The efficacy-related parameters, ESR and fibrinogen, also sustained decreases throughout siltuximab treatment in this study. Results after cycle 50 for efficacy-related laboratory parameters (C-reactive protein, ESR, and fibrinogen) and after cycle 43 for other reported laboratory parameters (triglycerides, neutrophils, platelets, and haemoglobin) should be interpreted with caution, because the number of patients with reported values is too small and inconsistent to draw meaningful conclusions. Prior to these timepoints, a stable decrease in efficacy-related parameters was observed, and all other reported parameters showed a consistent pattern of minor changes compared to baseline.

Blockade of IL6 signalling might increase the risk of infection by hindering the acute-phase response.[18] Despite its mechanism of action, patients treated with siltuximab had an exposure-adjusted incidence rate of serious infections of 20 per 1000 patient-years in the present trial, and 80 per 1000 patient-years in the phase 2 registration trial (compared with 200 per 1000 patient-years in the placebo group). Nonetheless, clinicians should be aware of the modestly increased risk of infection and the potential absence of symptoms in patients receiving this medication.[20]

Most haematological laboratory abnormalities were of grade 2 or lower. However, pretreatment monitoring of haematological parameters in all patients before initiating siltuximab is recommended.[9,21]

Increase of liver enzymes was recorded in two patients, leading to discontinuation in one patient. Transient increases of liver enzymes have been previously reported with siltuximab treatment.[12] A thorough medical examination before receiving siltuximab should identify at-risk patients. Patients with known hepatic impairment should be monitored, and any potential risks should be minimised by reducing alcohol intake, taking all medications at their recommended doses, and by enacting lifestyle changes such as healthy eating and regular exercise. Additionally, because increases in triglycerides were common, patients with risk factors for hyperlipidaemia (eg, obesity, body-mass index ≥30 kg/m², high blood pressure, and diabetes)[22] should be regularly monitored and treated with lipid-modifying drugs and enact lifestyle changes such as reducing intake of saturated or trans fats, regular exercise, and smoking cessation.

Because of the chronic nature of idiopathic multicentric Castleman disease[16] and the requirement for lifelong treatment,[17] some patients will probably have surgery during their treatment. Siltuximab did not interfere with recovery in the six patients that had surgery unrelated to idiopathic multicentric Castleman disease during the study.

Three patients had recorded anti-siltuximab antibodies, none of which were neutralising or affected activity and safety. These observations are not surprising given the chimaeric structure of siltuximab and are consistent with the continued long-term activity of the drug.[23,24]

Tocilizumab is a monoclonal antibody antagonist of soluble and membrane-bound IL6 receptor that is approved for the treatment of idiopathic multicentric Castleman disease in Japan, but not in the USA or Europe.[1] Evidence supporting the activity and safety of up to 5 years of treatment with tocilizumab was provided by a single-arm, Japanese study of patients with plasmacytic or mixed

histological type idiopathic multicentric Castleman disease.[23,25] However, differences in eligibility and response evaluation criteria between the siltuximab and tocilizumab studies preclude meaningful comparison of the two drugs.[9,12,23] For the treatment of idiopathic multicentric Castleman disease, tocilizumab is supported by a lower level of evidence than siltuximab and is recommended by the international consensus guidelines only in countries where siltuximab is not available or approved.[9]

The study enrolled patients who had completed either the phase 1 or 2 studies. Most of these patients (except for the three patients who were previously siltuximab naive) received siltuximab without disease progression and so were motivated to continue. Therefore, the study population was enriched for patients responding to and tolerant of the study medication, which is a recognised limitation of this type of extension trial. Nonetheless, the study design enabled assessment of the long-term safety and activity of siltuximab, while permitting continued access to siltuximab for patients appearing to benefit from this treatment.

This long-term safety extension study provides further evidence of the long-term safety and activity of siltuximab in the treatment of idiopathic multicentric Castleman disease, and supports the first-line use of siltuximab in this disease, as recommended in consensus guidelines.[9]

Contributors

All authors reviewed, drafted, or critically revised the manuscript and approved the final version. In addition, FvR was the principal investigator and contributed to the design of the extension study and writing of the manuscript; CC recruited patients and helped with the design of the extension study; and RK, PMV, and LEF were involved in recruiting participants.

Declaration of interests

FvR reports consultant fees from EUSA Pharma, Karyopharm, Takeda, Sanofi, and the Castleman Disease Collaborative Network and research funding from Janssen Pharmaceuticals and Bristol-Myers Squibb (BMS). CC is a member of the scientific advisory boards of Viracta Therapeutics, Curevo Vaccines, and OnCo Inc and is a consultant for EUSA Pharma. PMV reports consultancy fees from Novartis, Oncopeptides, Takeda, and TeneoBio; advisory board participation for BMS, Celgene, and Janssen; and speakers bureau participation for Amgen and Janssen. LEF reports no competing interests. DG and KK are employees of EUSA Pharma. RK has received research funding from Incyte, Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, Guardant Health, Grifols, Konica Minolta, and Omniseq; consultant fees from LOXO, X-Biotech, Actuate Therapeutics, Roche, and NeoMed; and speaker fees from Roche; and has equity in IDbyDNA and CureMatch.

Data sharing

De-identified participant data for the study will be made available immediately after publication, ending 3 years following article publication. Any requests for de-identified data and supporting materials (data dictionary, protocol, and statistical analysis plan) will be considered for any researchers who provide a methodologically sound proposal. Proposals should be directed to Karan Kanhai (karan.kanhai@eusapharma.com) in the first instance; to gain access, requestors will be required to sign a data access agreement.

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FIGURES AND TABLES

Table 1: Clinical benefit and disease control assessment for Castleman's disease

	Improved	Stable	Worsening
Haemoglobin	≥2 g/dL increase from baseline without transfusion	<2 g/dL variance relative to baseline without transfusion	≤2 g/dL decrease from baseline without transfusion
Fatigue	≥1 CTC grade point decrease from baseline	No change in CTC grade relative to baseline	≥1 CTC grade point increase from baseline
Anorexia	≥1 CTC grade point decrease from baseline	No change in CTC grade relative to baseline	≥1 CTC grade point increase from baseline
Fever*	≥2°C decrease from baseline or return to normal body temperature (37 °C)	<2 °C variance relative to baseline unless normal body temperature is achieved, then define as improved	≥2 °C increase from baseline
Weight	≥5% decrease from baseline (without new oedema or increase in existing oedema)	<5% variance relative to baseline (without new oedema or an increase in existing oedema)	≥5% decrease from baseline (weight loss not due to decreased oedema)
Size of largest lymph node†	≥25% decrease (bidimensionally) from baseline measured by CT or physical examination	No increase or decrease of ≥25% (bidimensionally) from baseline measured by CT or physical examination	≥25% increase (bidimensionally) from baseline measured by CT or physical examination

Table 1 legend: Patients were categorised as having improved disease, stable disease, or disease progression on the basis of the combination of these components. If a patient improved in one or more component and remained stable for the others, the subject was considered to have improved. A worsening in any component was considered disease progression. If a patient showed disease progression at two consecutive assessments, they had to discontinue study treatment. CTC=common terminology criteria.

*Fever was assessed in conjunction with patient-reported night sweats. †In patients with cutaneous disease, the lymph node component should be replaced by the physician's global assessment of disease, with the extent of disease estimated by body surface area.

Table 2: Patient baseline demographics and disease characteristics

	Siltuximab (n=60)
Age	
Median (IQR), years	45·0 (35.8–56.0)
<65 years	55 (912%)
Sex	
Women	20 (33%)
Men	40 (67%)
Race	
White	31 (52%)
Black	3 (5%)
Asian	23 (38%)
Other	3 (5%)
Median weight, kg	68·5 (58.9–90.1)
Patients with newly diagnosed Castleman's disease (no previous systemic therapy)	22 (37%)
ECOG Performance score*	
0	20 (33%)
1	33 (55%)
≥2	7 (12%)
Histology†	
Hyaline vascular	15 (25%)
Plasmacytic	24 (40%)
Mixed	21 (35%)
Mean time from diagnosis to first siltuximab administration, years	2·20 (3·4)
Prior therapy‡	
Cancer-related surgery	11 (18%)
Systemic therapy regimens	38 (63%)
Rituximab	12 (20%)
Cyclophosphamide	12 (20%)
Corticosteroid	6 (10%)
Thalidomide	3 (5%)
Other	5 (8%)

Table 2 legend: Data are median (IQR), n (%), or mean (SD). Patient demographics at baseline refer to demographics collected in either phase 1 or phase 2 studies, reported as n (%). ECOG=Eastern Cooperative Oncology Group. *Karnofsky performance status was collected in the phase 1 study and converted to ECOG score using an estimated conversion method. †Histology is based on local pathology review. ‡Previous therapy refers to therapy recorded in both phase 1 and phase 2 studies.

Table 3: Adverse events attributed to siltuximab (n=60)

	Grade 1–2	Grade 3	Grade 4
Metabolism and nutrition disorders	19 (32%)	5 (8%)	0
Hypertriglyceridaemia	11 (18%)	2 (3%)	0
Hypercholesterolaemia	9 (15%)	0	0
Hyponatraemia	0	1 (2%)	0
Hypophosphataemia	0	1 (2%)	0
Hypocalcaemia	0	1 (2%)	0
Infections and infestations	20 (33%)	3* (5%)	0
Upper respiratory tract infections	9 (15%)	0	0
Herpes zoster	3 (5%)	1 (2%)	0
Flu	0	1 (2%)	0
Rectal abscess	0	1 (2%)	0
Tracheobronchitis	0	1 (2%)	0
Gastrointestinal disorders	20 (33%)	1 (2%)	0
Diarrhoea	6 (10%)	1 (2%)	0
Skin and subcutaneous tissue disorders	19 (32%)	0	0
Maculopapular rash	9 (15%)	0	0
Pruritus	8 (13%)	0	0
Blood and lymphatic system disorders	13 (22%)	5 (8%)	1 (2%)
Neutropenia	5 (8%)	3 (5%)	1 (2%)
Lymphopenia	1 (2%)	1 (2%)	0
Polycythaemia	0	1 (2%)	0
General and administration site disorders	9 (15%)	0	0
Fatigue	7 (12%)	0	0

Table 3 legend: Data are n (%). Patients with treatment-emergent adverse events of grades 1–2 (occurring in ≥10% of patients) or grade ≥3 (all) considered at least possibly attributed to siltuximab. *Grade 3 cases of flu and tracheobronchitis occurred in the same patient.

Table 4: Patients with long-term disease control for up to 6 years on the basis of investigator assessment

	Siltuximab (n=60)
Patients with disease control at their last on-study assessment*	58 (97%)
Patients with disease control after 6 years†	42 (70%)
Patients who discontinued before 6 years	18 (30%)
Pursued local siltuximab	8 (13%)
Withdrawal of consent	4 (7%)
Adverse events	2 (3%)
Progressive disease	2 (3%)
Pregnancy	1 (2%)
Physician's decision‡	1 (2%)

Table 4 legend: Disease control data were collected in the present study only; patients must not have had disease progression while receiving siltuximab. Disease control is defined as a stable or better response and no worsening in the six clinical parameters. *58 (97%) of 60 patients reported disease control at their last assessment; however, some of these patients discontinued before the 6-year data cutoff point. †All patients who completed the trial up to the 6-year data cutoff had disease control; patients who discontinued before were counted as treatment failures. ‡Based on the requirement for growth factors to overcome persistent neutropenia.

Figure: Study profile

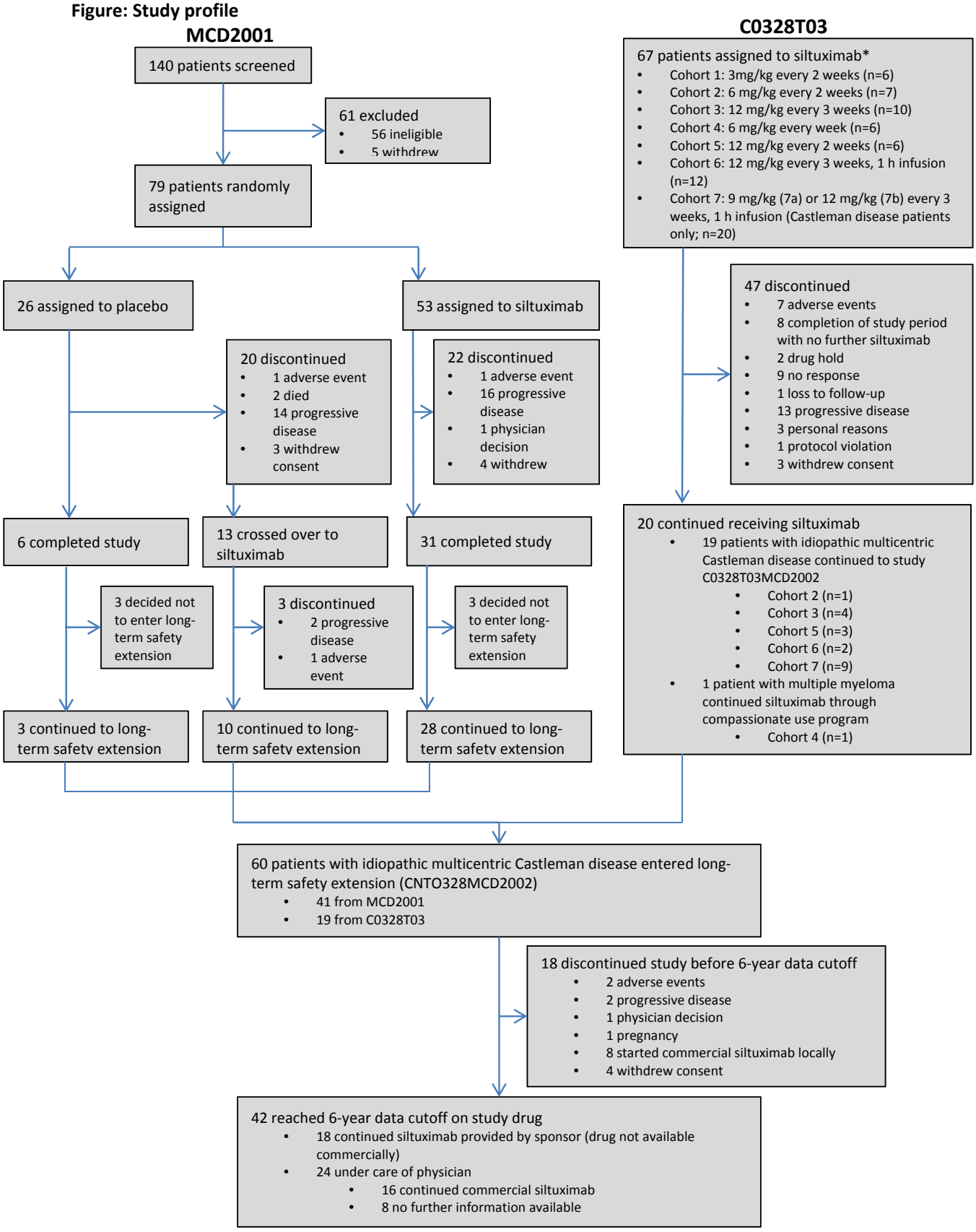

Figure legend: *17 with non-Hodgkin lymphoma, 13 with multiple myeloma, and 37 with Castleman disease, of whom 35 had idiopathic multicentric Castleman disease and two had unresectable unicentric Castleman disease.